

## Significance of Inflammatory Biomarkers in Peripheral Arterial Disease Diagnosis and Prognosis

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### Abbreviations

PAD: Peripheral Arterial Disease

Peripheral arterial disease (PAD) is a widespread group of vascular diseases, due to arterial stenosis or occlusion, in which blood flow in the affected limbs is reduced. It is estimated that PAD affects more than 230 million people worldwide. Due to the large number of asymptomatic PAD cases (>50% of PAD patients), it is difficult to accurately estimate the PAD prevalence. PAD is associated with traditional atherosclerosis risk factors, including age, smoking, dyslipidemia, arterial hypertension, diabetes mellitus, etc. In women, the PAD incidence is similar only in old age, whereas in patients under 65 years - it is reduced by about half, compared to men [1-6].

Atherosclerosis is the most common PAD etiology and accounts for >90% of PAD cases. Two main pathophysiological processes are involved in the atherosclerotic plaques progression: (1) gradual accumulation of lipids, monocytes, and fibers in the arterial intima and (2) endothelial cell apoptosis followed by atherosclerotic plaque rupture. Vascular remodeling and collateral circulation are natural compensatory mechanisms, in order, to reduce the consequences of the vascular narrowing on the circulating flow [7,8].

Endothelial dysfunction is one of the main processes underlying the vascular atherosclerotic lesions development. In recent dec-

ades, for early PAD diagnosis and PAD prognosis evaluation, acute and chronic inflammatory plasma biomarkers (acute phase reactants, markers of endothelial dysfunction, endothelial progenitor cells, inflammatory cytokines, etc.) have been proposed. Unfortunately, there are no ideal biomarkers, neither for PAD diagnosis, nor for therapeutic response monitoring. Importantly, inflammatory biomarkers have proven to be significant in PAD Leriche-Fontaine stages stratification, especially if coexisting diseases limiting the walking distance estimation are present (e.g., heart failure, decompensated cirrhosis, chronic obstructive pulmonary disease, diabetic sensorimotor peripheral neuropathy, degenerative hip osteoarthritis, gonarthrosis, lumbago, *claudicatio spinalis*, lymphedema, etc.) [5,7,9-11].

Moreover, in recent decades, several studies have shown the importance of long time PAD patients evaluation, in order to identify the practical utility value among the inflammatory biomarkers as predictors for PAD. One of these biomarkers is the C-reactive protein, which is a "benchmark" in the study of various «classic» (e.g., fibrinogen, erythrocyte sedimentation rate, interleukins, etc.) and «novel» (e.g., cistatin C, neopterin,  $\beta$ 2-microglobulin, copeptin, etc.) biomarkers, which have proven their importance in predicting unfavorable prognosis in PAD patients [12-16].

Therefore, early PAD diagnosis using complex methods (anamnesis, clinical manifestations, ankle-brachial index, specific bi-

omarkers, etc.) at preclinical stages, and initiation of a integrated approach program for PAD patients (combating existing risk factors and initiating specific non-pharmacological, and pharmacological preventive therapy), will reduce the disability degree, will increase the life quality, and will improve the PAD patients prognosis. However, currently, no inflammatory biomarker has been found in clinical practice that would reflect accurately the PAD presence, as single test. Future research should focus not only on individual biomarkers study in PAD, but also on a multimarker approach, using combinations of various biomarkers.

### Authors Contribution

All authors have read and agreed to the published version of the manuscript. All authors contributed equally to this work.

### Conflict of Interest

The author declares no potential conflicts of interest.

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